Section of Obstetrics and Gynæcology

President—EARDLEY HOLLAND, F.R.C.S.

[*March* 15, 1935 *contd*]

A Follow-up Survey of the Cases of Hydatidiform Mole and Chorion-epithelioma treated at the London Hospital since 1912

By ALAN BREWS, F.R.C.S.

THIS paper is based on a consecutive series of 72 cases of hydatidiform mole and 16 cases of chorion-epithelioma obtained from the obstetric, gynæcological, medical, and surgical case-records of the London Hospital. Some of the cases of hydatidiform mole subsequently developed chorion-epithelioma and these are included in the latter series.

HYDATIDIFORM MOLE

Ætiology.—Only one case (Case 5) throws any light on the ætiology of hydatidiform mole. The patient, aged 30, had three children, the youngest eight years ago. Her last normal period was fourteen weeks before admission, and she was admitted because of vaginal hæmorrhage for nine weeks. After two weeks' conservative treatment in hospital, it was decided to induce abortion surgically, as vaginal bleeding persisted. This was done by inserting laminaria tents and packing the cervical canal and vagina with sterile gauze. After forty-eight hours the patient spontaneously aborted a fœtus attached to a complete normal placenta and, in addition, a hydatidiform mole, which appeared to be entirely separate. The original mole was considerably larger than the placenta attached to the fœtus. This case definitely suggests that the factor inducing the formation of hydatidiform mole lies in the ovum rather than in any abnormality, endocrine or otherwise, of the mother. Madame Boivin, Birnbaum, Falgowski and Lukens, amongst others, have recorded similar cases in the literature.

Age Incidence.

Patients under 20 years	2
,, 20-29 years	26
,, 30-39 ,,	17
,, 40-49 ,,	19
,, 50 years, or more	8
	72

It is of interest that 27 patients were over 40 years of age, i.e. 37·5%.

Previous Pregnancies.

Primigravida	17
1-10 children	39
Over 10 children	10
No notes of previous pregnancies	6
	72

In the 66 cases in which notes of previous pregnancies are available, there is a total of 283 children and 43 miscarriages. This is an average fertility of 4·3 children and 0·7 miscarriages.

Symptomatology.

The presenting symptom was:—

Abnormal uterine hæmorrhage	in 59 cases
Vomiting	in 4 ,,
Abdominal pain	in 3 ,,
Swelling of feet; headaches	in 2 ,,
Abdominal enlargement	in 1 case
No note	in 3 cases
	72 cases

Duration of amenorrhœa before the onset of bleeding.

Bleeding one month or less after last menstrual period	7 (10%)
Amenorrhœa one to three months	42 (60%)
Amenorrhœa three to nine months	11
Amenorrhœa one year or more	2
Unrecorded	10
	72

Size of uterus in comparison with apparent duration of pregnancy.

Part or whole of mole passed before admission	20 cases
Unrecorded	15 ,,
	35 cases

Therefore, in the 37 cases in which the duration of pregnancy and the size of the uterus before any mole was expelled are recorded:—

In 24 cases the uterus was bigger than one would have expected	64·8%
In 5 cases it was correct in size	13·6%
In 8 cases it was smaller than one would have expected	21·6%

Briggs and Essen-Moller have observed, in many cases, the uterus to be smaller than the normal for the duration of pregnancy.

Albuminuria.

No albumin	25
Albumin up to heavy cloud on boiling	7
Large amounts of albumin	5
Unrecorded	35
	72

Therefore albumin in urine in 12 cases out of 34 examined = 35%.
Also No. 26, pus; No. 34, culture, *Bacillus coli communis*. No. 71, culture, streptococci

The large number of cases in which urine was not recorded as having been examined is presumably due to the impossibility of obtaining a specimen for examination without the passage of a catheter, as the majority of patients were actually bleeding vaginally on admission.

Differential diagnosis.

The original diagnosis was:—

Some type of abortion	in 36 cases
Placenta prævia	in 2 ,,
Menorrhagia (1 case) P.M.H. (1 case) i.e. abnormal uterine hæmorrhage in 40 cases.	in 2 ,,
Fibroids	in 6 ,,
Fibroids and normal pregnancy	in 1 case
Ovarian cyst	in 1 ,,
Ovarian cyst and normal pregnancy i.e. pelvic tumour in 9 cases.	in 1 ,,
Neurotic vomiting	in 2 cases
Correctly diagnosed before vesicles escaped	in 4 ,,
Normal pregnancy and chronic nephritis	in 1 case
	56 cases

In the remaining 16 cases the diagnosis was certain, as typical hydatidiform mole had escaped or was escaping on admission.

Much the commonest error in diagnosis was that of ovarian or uterine tumour (8 cases). Most of these errors occurred in the patients over 40 years of age in whom short periods of amenorrhœa and irregular uterine hæmorrhage were liable to be regarded as menopausal symptoms. In one other case the original diagnosis of ovarian cyst and normal pregnancy was correct, in so far as there were bilateral large multilocular lutein cystomata of the ovaries plus a uterus enlarged by the presence of hydatidiform mole.

(In Findley's 500 cases from the literature 11·6% had cystic ovaries.)

Treatment.

General anæsthetic, manual expression, digital separation, removal with ovum forceps	27 cases
Majority of mole spontaneously expelled; remaining fragments digitally removed because of persistent bleeding	13 ,,
Spontaneous expulsion complete; operative assistance unnecessary	9 ,,
Surgical induction of abortion of mole with laminaria tents and gauze packing	8 ,,
Surgical induction with small rubber bag	1 case
Surgical induction by vaginal hysterotomy	1 ,,
Dilatation and curettage. (Mole expelled usually some weeks previously)	5 cases
Sub-total hysterectomy	4 ,,
Pan-hysterectomy	2 ,,
Laparotomy, bilateral ovariotomy, and subsequent spontaneous abortion of the mole per vaginam	1 case
Death of patient from hæmorrhage, mole still *in utero*	1 ,,
	72 cases

Primary mortality P.M. 375/1922.—In this series of 72 cases there has been only one death directly attributable to the mole pregnancy. This was case 43, a woman 36 years of age who had had three children. Her last normal period was three months before admission and she complained of slight daily vaginal bleeding for eight weeks and severe bleeding for twenty-four hours; the history being that the blood had soaked through two mattresses. She was moribund from anæmia on admission. Intravenous saline was given at once, but she died before a blood transfusion could be carried out. The uterus reached 2 in. above the umbilicus and there was about half-a-pint of bleeding in hospital before the cervix could be plugged. The post-mortem examination showed acute anæmia of all organs, and in the uterus a large benign hydatidiform mole.

The hydatidiform mole mortality as published shows considerable variation.
Findley: 265 benign hydatidiform moles. 28 died = 10·5%.
Gordon: Mortality 9%. De Lee: 16%.
Sande: 5% of 122 cases of hydatidiform mole died.
Dorland: 100 cases of hydatidiform mole % from literature; 10% mortality. 3% hæmorrhage at time of operation; 2% perforation of uterus; 5% infection.

The low mortality rate in the present series—1·4%—may be fortuitous in so far as the series consists of relatively few cases but is largely the result of the methods of treatment adopted.

Convalescence.

Pyrexia: In six cases the temperature charts are not available. Those of the remaining 66 cases may be divided into the following groups:—

Afebrile	24	
Febrile to a degree not above that of minimum puerperal morbidity	17	
Moderate pyrexia lasting up to 14 days	19	
Pyæmia	2	9%
Septicæmia	4	
	66	

Case 25.—Digital evacuation of mole from uterus: Pyrexia 99-104, settled fourth week. Blood-culture sterile, third week. Abscess in back, pus grew streptococci. Swelling of left shoulder and first metacarpophalangeal joint, subsided spontaneously.

Case 34.—Digital evacuation of mole from uterus: Pyrexia seven weeks. Blood-culture twice sterile; deep abscesses right and left thighs, pus grew streptococci.

Case 45.—Spontaneous evacuation of mole: Remittent and intermittent pyrexia up to 101° *nocte* for ten weeks. Blood-culture twice sterile; subinvoluted uterus. Discharged herself, still febrile.

Case 52.—Exploration of uterus: Four rigors in fourteen days after exploration of uterus. Blood-culture sterile; then pan-hysterectomy for chorion-carcinoma.

Case 54.—Digital exploration of uterus; uterus packed sterile gauze: Twenty-three rigors in four weeks; blood-culture twice sterile. Temperature settled seventh week.

Case 59.—Vagina packed before mole was expelled spontaneously: Pyrexia up to 102·5 for four weeks; then second post-partum hæmorrhage; chorion-carcinoma. Pan-hysterectomy.

Two of the cases complicated by puerperal septicæmia developed chorion-epithelioma.

Secondary Hæmorrhage.

Six patients were treated primarily by hysterectomy; none of these developed post-operative hæmorrhage, as a complication, and in one other case the patient died before the mole was expelled.

Of the 65 remaining cases ten developed abnormal uterine hæmorrhage within a few weeks of the expulsion of the mole, i.e. 15%. In each case the uterus was explored, or re-explored, and fragments of tissue were sent for histological examination.

In six cases (27, 40, 50, 52, 59 and 64) the histological report was chorion-epithelioma and pan-hysterectomy was performed. In four of these cases (27, 50, 52, 59) subsequent examination of the uterus confirmed the diagnosis of chorion-epithelioma.

Complete investigation of these ten cases resulted in the following findings and treatment :—

Treated by curettage followed by pan-hysterectomy	Chorion-epithelioma	in 4 cases
	Retained tissue histologically suggestive of chorion-epithelioma	in 2 ,,
Treated by curettage only	Retained fragments of benign mole	in 2 ,,
	Functional abnormal uterine hæmorrhage not associated with retained mole or developing chorion-epithelioma ..	in 2 ,,
		10 cases

Case 27.—Aged 31 years; married two years ; no previous pregnancies. Five months before admission, when four and a half months pregnant, spontaneously expelled a hydatidiform mole. For six weeks before admission had continuous slight brown vaginal discharge, also occasional short brisk hæmorrhages. Exploration of the uterus revealed some enlargement of the left cornu. Curettage was performed and the tissues removed were sent for histological examination. The report was blood-clot, fibrin, and a few masses of atypical luxuriant chorionic epithelium.

In view of these findings, five months after the spontaneous evacuation of the mole a pan-hysterectomy was performed by Mr. Gordon Luker. The uterus after removal showed two small areas of infiltrating chorion-epithelioma in the fundus of the uterus. Histological examination confirmed this diagnosis. A section of one ovary showed abnormal excessive lutein tissue formation in the right ovary, which was not abnormally large.

Follow-up.—This patient was alive and well thirteen years later.

Case 50.—Aged 44 years; seven children, last nearly four years ago; no miscarriages. Last menstrual period five months ago. Six weeks before admission continuous vaginal bleeding for seven days, and since then for three or four hours every three or four days.

On examination: Large uterus reaching above umbilicus. Spontaneously aborted mole immediately after admission.

Histological report.—Hydatidiform mole. Chorionic epithelium very luxuriant in connexion with many villi.

Twelve days later, still red lochia. Uterus explored. A little irregularity on right side of fundus felt, but no definite retained fragments of mole found. Patient transferred to a convalescent home, but twenty-nine days after mole delivered, she had a very sudden profuse vaginal hæmorrhage whilst walking in the grounds. She was returned to bed almost pulseless and when fit was transferred back to hospital. Thirty-three days after the expulsion of the mole, i.e. four days after the severe secondary hæmorrhages, Mr. Eardley Holland performed an abdominal pan-hysterectomy. The uterus has been lost, but it is recorded that a small

area of typical chorion-epitheliomatous growth was found in the right cornu. A microscopic section through this region showed chorion-epithelioma invading the wall of the uterus.

Follow-up.—This patient was alive and well, with no clinical evidence of recurrence eight years later.

Case 52.—Aged 30 years; one child four years ago; one miscarriage at three months four weeks ago. Her doctor estimated the miscarriage at about four months, but no fœtus was seen; red loss ceased after fourteen days. After twelve days without any bleeding, daily hæmorrhages recurred for eight days before admission. She was admitted for exploration of the uterus under the diagnosis of incomplete abortion. A sound was passed 5 inches and an unusual mass was found in the wall of the fundus uteri; some vesicles were removed when the uterus was explored with ovum forceps. The tissue removed was examined histologically and proved to be portions of the myometrium infiltrated by malignant hydatidiform mole (chorion-epithelioma).

Fifteen days later Dr. Russell Andrews performed a pan-hysterectomy. At the operation a secondary deposit was felt in the wall of the vagina, but was not removed.

The uterus showed a typical chorion-epitheliomatous growth in the posterior wall of the upper part of the uterus, confirmed by histological examination.

Follow-up.—This patient was alive and well nine years later.

Case 59.—Aged 49 years; four children, the last four years ago; two miscarriages, the last nine years ago. For eight months periods irregular; longest period of amenorrhœa two months. Sent up as an obstetric emergency under the diagnosis of placenta prævia.

On admission: Very anæmic; still bleeding. Fundus uteri, twenty-eight weeks. No fœtus palpable or audible; cloud of albumin in urine on boiling; blood-pressure 180/90. Cervix dilated one-fifth. A few vesicles removed digitally. Spontaneous expulsion of mole the day after admission, the cervix and vagina having been packed with flavine gauze. Subsequently intermittent pyrexia up to 102·5°. Lochia ceased normally, but thirty-two days after expulsion of mole sudden secondary hæmorrhage of about half a pint.

Forty-one days after expulsion of mole, uterus explored with a blunt curette. Tissue removed from a soft area on left side of region of internal os. This showed a number of fragments of myometrium and hypertrophied endometrium, some invaded by chorion-epithelioma. Fifty-seven days after expulsion of mole, pan-hysterectomy was performed by Mr. Victor Lack.

The uterus showed two focal areas where the myometrium was invaded by chorion-epithelioma. The slide taken from the larger growth at the left of the internal os confirms the diagnosis of chorion-epithelioma.

Follow-up.—This patient was alive and well more than five years later.

In the other two cases (40, 64) in which the report on the curettage after secondary hæmorrhage was chorion-epithelioma, pan-hysterectomy was performed, but no growth was found in either uterus.

(Whitridge Williams states that a permanent cure may occasionally follow a simple curettage.)

Case 40.—Aged 47 years; ten children. Three months' amenorrhœa, followed by the abortion of a hydatidiform mole. Admitted to hospital; uterus cleared digitally. Readmitted six weeks' later, as two floodings had occurred; the second, on the day of readmission being very severe—(alleged several pints). Curettage was performed by Mr. Victor Lack. Sound passed 2½ inches; several vesicles and much blood-clot removed. The histological report was chorion-epithelioma. As a result, pan-hysterectomy was performed (Gordon Luker). Macroscopically a small flat growth, of the size of a florin in diameter, appeared to be present high up on the posterior wall of the uterine cavity. Histologically there was no evidence of any chorion-epithelioma in this or in other parts of the uterus. Theca lutein cysts were present in both ovaries.

Follow-up.—This patient was alive and well ten years later.

Case 64.—Aged 50 years; six children. Last menstrual period seven months ago. Two months ago, blood-stained discharge for two days. Admitted as an emergency with severe vaginal bleeding for several hours. Uterus just above umbilicus. Spontaneous abortion of a large hydatidiform mole. Six weeks later readmitted for curettage. A little blood-stained discharge on two occasions three weeks after leaving hospital; nil since. Curettage was reported as chorion-epithelioma, and three weeks later a pan-hysterectomy was performed by Mr. Eardley Holland. There was no macroscopic or microscopic evidence on examination of the uterus of chorion-epithelioma.

Follow-up.—This patient remains alive and well four years later.

In two cases (31, 41) the histological report was retained fragments of benign mole. Both have been followed up and they were alive and well thirteen and eleven years later respectively. In two cases (47, 72) the histological report was fragments of endometrium only. The second patient had, in addition, a negative Zondek-Aschheim reaction. Both patients remain well, respectively nine years and six months later. (The Friedmann test in the latter case was also negative.)

In 20 other cases in which there had been no excessive or abnormal uterine hæmorrhage or discharge a prophylactic exploration of the uterus and curettage was carried out six to twelve weeks later in order that chorion-epithelioma, if present, might be diagnosed as early as possible. In no case was there any macroscopic or microscopic evidence of chorion-epithelioma and in no case is chorion-epithelioma known to have developed at a later date.

Incidence of Chorion-epithelioma following Hydatidiform Molar Pregnancy

In addition to the four cases described under secondary hæmorrhage, there were two other definite cases that developed chorion-epithelioma:—

Case 49.—Aged 45 years; four children, last nineteen years ago. Last menstrual period eleven weeks ago. Five weeks and three and a half weeks ago slight vaginal bleeding for a few hours. Two days' severe bleeding and vomiting. Anæsthetic; placental remains digitally removed; cavity swabbed out with iodine and packed with gauze. Discharged after one week in hospital. Readmitted ten weeks later. Slight irregular periods since last admission. Seven weeks' dull, aching pain in lower abdomen. Twenty-four hours before admission, began to bleed from vagina. Sixteen hours before admission, onset of severe abdominal pain, vomiting, and difficulty in micturition. *On admission*: Ill; anæmic; chest clear; general abdominal tenderness and rigidity with indefinite lump in left lower quadrant. Lump the size of a tangerine orange in the pouch of Douglas. Emergency laparotomy (performed by Mr. Gordon Luker.) Much free blood in the abdomen, in which was found a mass of hydatidiform mole lying free. A hole was found below and behind the right cornu of the uterus through which more mole could be seen. Pan-hysterectomy was performed.

Follow-up.—This patient was alive and well eight years later. A microscopic section through the edge of this perforation shows hydatidiform villi covered by excessive infiltrating trophoblast (chorion-epithelioma).

Case 3.—Aged 31 years; single. Four months' amenorrhœa, followed by bleeding and the spontaneous abortion of a hydatidiform mole, ten days before admission. Admitted because of slight continuous vaginal bleeding since then. The mole was sent for examination and shows the features of a benign hydatidiform mole.

The uterus reached nearly up to the umbilicus, but on exploration contained nothing but blood-clot and a little débris. She was readmitted six weeks later for diagnostic curettage, in case an early chorion-epithelioma should be present. (There had been no bleeding or discharge.) Histologically this curettage revealed nothing more than normal endometrium and menstrual débris. Twenty-four weeks after the spontaneous abortion of the mole, there was an onset of constant pain, low down in the back and worse at night. Patient was no

better after complete rest in bed for one month. Bowels open only once every two or three days since the mole was aborted, but on readmission thirty weeks later the patient complained of rectal incontinence. There was a pleural effusion over the right lower lobe of the lungs and the aspirated fluid was blood-stained and contained polymorphonuclear leucocytes and endothelial cells. The temperature was intermittent during nearly two months that she was in hospital, 98°—102°. Nine months after the mole was expelled the patient suddenly became unconscious and died half an hour later.

A post-mortem examination revealed: (1) In the uterus and vagina, no macroscopic or microscopic evidence of hydatidiform mole or chorion-epithelium; (2) primary chorion-epithelioma of the rectovaginal septum and presacral tissues; (3) disseminated secondary growths of chorion-epithelioma in many organs, especially lungs and liver.

Spontaneous perforation of a subarachnoid vein by a malignant deposit caused a fatal subdural hæmorrhage.

One other case (24) should be mentioned:—

Patient, aged 36 years; two children, aged 13 years and 8 years respectively.

Six weeks before admission, three months' miscarriage. Since then uterus explored and cleared out three times because of repeated hæmorrhages. On admission uterus explored a fourth time. The histological report on this curettage was dropsical villi covered with excessive chorion-epithelium and numerous giant cells in the decidua. No definite evidence of chorion-epithelioma, but appearances suggestive of malignancy well marked.

Pan-hysterectomy performed by Mr. Gordon Luker; large irregular greenish-white ulcer found in the endometrium.

Three sections from the wall of the uterus show doubtful chorion-epithelioma and very atypical decidual hyperplasia.

Follow-up.—This patient could not be traced. The pathological condition is one to which the old name for chorion-epithelioma "deciduoma malignum" might reasonably be applied.

SUMMARY OF THE INCIDENCE OF CHORION-EPITHELIOMA IN THIS SERIES OF 72 CONSECUTIVE CASES OF HYDATIDIFORM MOLE

Primary mortality from hæmorrhage		1 case
Primary hysterectomy.	Pan-hysterectomy .. 2	6 cases
	Sub-total hysterectomy ... 4	
Untraced		17 ,,
Traced—no evidence of chorion-epithelioma		39 ,,
Death from disseminated chorion-epithelioma eight months after abortion of hydatidiform mole (uterus—not removed)		1 case
Secondary pan-hysterectomy of chorion-epithelioma. Definite growth in uterus removed		5 cases
Secondary pan-hysterectomy for malignant hydatidiform mole. Doubtful evidence of chorion-epithelioma in uterus		1 case
Secondary pan-hysterectomy for chorion-epithelioma. No growth in uterus removed		2 cases
		72 cases

(Incidence of chorion-epithelioma, 6 cases = 8·3%.)

The relationship between hydatidiform mole and chorion-epithelioma has been frequently referred to in the literature.

Findley, 500 cases; 157 developed chorion-epithelioma (31·4%).

Pallosson and Violet, 455 cases; 203 chorion-epithelioma (44%).

Novak, only 1% of hydatidiform moles became chorion-epithelioma.

Senarcleus, 49 hydatidiform moles. 13% became chorion-epithelioma.

Many of these figures are not comparable with the incidence of 8·3% in the present series, because they are derived from an analysis of collections of individual cases, or small groups of published cases, and not from a consecutive series from one large hospital.

Conservative treatment of hydatidiform mole.—In the 40 traced cases in which the uterus was not removed, either primarily or secondarily, the conservative treatment adopted must be justified or condemned on the following findings :—

One patient died eight months later from disseminated chorion-epithelioma, the primary growth being in the cellular tissues around the rectum, and not in the uterus.

Thirty-nine patients subsequently developed no evidence of chorion-epithelioma. Many of them were of early child-bearing age at the time of the molar pregnancy, and 17 who subsequently became pregnant had among them 37 children and 11 miscarriages. No evidence was obtained to suggest that any of the miscarriages were hydatidiform moles.

Pregnancy tests : their value in diagnosis, prognosis, and treatment.—The pregnancy tests are now available as an additional method of assisting prognosis. It is only in the last two cases of this series that the Zondek-Aschheim and Friedman tests of pregnancy have been employed.

Case 71.—The pregnancy test findings in this case are of considerable interest, especially in their interpretation in relation to prognosis and treatment.

The patient, aged 21 years, had been married eighteen months, and this was her first pregnancy. Her last period was fourteen weeks before admission.

Her symptoms on admission may be summarized as follows : Six weeks' morning vomiting : two weeks, vomiting everything. Four weeks before admission, brown discharge for three days : three weeks before admission, slight bleeding for one day ; one week before admission, bleeding like a menstrual period.

Loss of weight about 1 st.

Physical signs on admission : Pale ; very thin : breasts active ; nothing abnormal discovered on clinical examination of the chest.

Uterus enlarged to size of twenty-four weeks' pregnancy. (Last menstrual period fourteen weeks ago.)

Fœtus not felt ; fœtal heart not heard.

Trace of albumin in urine. Blood-pressure 135/75.

Blood-count : Secondary anæmia. R.B.C. 3,700,000 ; C.I. 0·9 ; W.B.C. 6,800 ; 74% polymorphonuclear leucocytes.

Sputum : No tubercle bacilli or chorionic tissues.

X-ray examination : Chest clear. No fœtus visible in abdomen or pelvis.

Pregnancy tests : Day of admission, Zondek-Aschheim, strongly positive. (0·4 c.c. injected twice on first day, three times on second day, and once on third day ; mice killed after 100 hours. Total urine detoxicated with ether 2·4 c.c.)

Seven days after admission, Friedman test positive ; quantitative Zondek-Aschheim positive in dilutions of 1 : 25, 1 : 100, 1 : 200.

Fourteen days after admission, uterus explored. Hydatidiform mole vesicles found. Four laminaria tents inserted in cervix ; vagina packed.

Next day, after the injection of 5 units of pituitrin twice in an interval of two hours, strong uterine contractions began. Mole digitally evacuated and bimanually expressed from uterus under anæsthetic. Considerable bleeding, controlled by hot douche, pituitrin and ergotoxin. As a result the blood-count dropped from 3,400,000 red cells with colour-index 0·9 to 2,400,000 with colour-index 0·7.

Histological report : Hydatidiform mole ; no definite evidence of malignancy.

Seven weeks after evacuation of the mole the patient was discharged from hospital. The clinical findings at that time were : General condition much improved ; no vomiting ; gain in weight ½ st. ; urine clear ; blood-pressure 125/80. Cough less ; no sputum. No vaginal bleeding or discharge. Uterus involuting well ; still a little bulky.

Blood-count : R.B.C. 4,000,000 ; C.I. 0·86.

Pregnancy tests : Friedman, positive. (10 c.c. of ether-detoxicated urine injected twice with an interval of twenty-four hours, intravenously. Rabbit killed after fifty hours.)

Quantitative Zondek-Aschheim : Undiluted urine, positive. Urine diluted 1/25, negative ; 1/100, negative ; 1/200, negative.

The patient was watched, as carefully as she would allow, in the gynæcological follow-through department with the following results:—

Fourteen weeks after evacuation of the mole: General condition improving; still gaining weight; good colour. Still occasional cough; sputum sometimes blood-stained; five weeks' slight daily vaginal bleeding.

Pregnancy tests: Friedman, positive. Quantitative Zondek-Aschheim, undiluted positive; diluted 1/25; 1/100; 1/200, negative.

Because of these findings she was admitted at once for a diagnostic curettage. Histological report: Fragments of necrosed tissue and blood-clot from the uterus. No recognizable tissue except a small fragment of inflamed endometrium; a few scattered large cells and one structure like the skeleton of a necrosed vesicular chorionic villus.

Eighteen weeks after the evacuation of the mole and four weeks after the diagnostic curettage her general condition was still excellent; there was no cough, and all vaginal bleeding and discharge had ceased a few days after the curettage. The uterus was well involuted, mobile, and anteverted.

Pregnancy test: Friedman, positive.

Twenty-two weeks after the evacuation of the mole no alteration in symptoms and physical signs since last examination.

Pregnancy tests: Friedman, positive. Quantitative Zondek-Aschheim, undiluted, positive; diluted 1/25, 1/100 negative.

Thirty-nine weeks (*nine months after evacuation of the mole*): General condition of the patient excellent, no symptoms: perfectly normal regular menstrual periods since last visit (four in all). No abnormal physical signs.

Pregnancy test: Friedman, negative.

Table I summarizes the pregnancy test findings in this case.

TABLE I.—PREGNANCY TEST FINDINGS IN CASE 71

Time when pregnancy tests were made	Results: Friedman		Zondek-Aschheim		
		1/1	1/25	1/100	1/200
2 weeks before evacuation of mole...		++			
1 week before evacuation of mole ...	+		−	−	−
7 weeks after evacuation of mole ...	−	−	−	−	−
14 weeks after evacuation of mole ...	−	−	−	−	−
Curettage					
18 weeks after evacuation of mole ...	−				
22 weeks after evacuation of mole ...	−	−	−	−	−
Menstruation recommenced					
39 weeks after evacuation of mole ...	−	−	−	−	−

It is of interest to recall here that:—

(1) Schmorl, 1904, found chorionic cells in 80% of 158 women dying at different stages of normal pregnancy.

(2) A fatal case of hydatidiform mole with multiple small syncytial infarcts of the lungs was recorded by J. E. Hughes (*Proc. Roy. Soc. Med.*, 1930, xxiii, 33-35).

(3) Professor James Miller at a meeting of the Edinburgh Obstetric Society recorded a fatal case of hydatidiform mole, in which entire chorionic villi were recognized in the lungs.

(4) T. G. Stevens (*Clin. Journ.*, 1927, lvi, 133-36) recorded a case of hydatidiform mole with multiple lung trophoblastic metastases and death from hæmoptysis after intravenous saline.

In case 72 the pregnancy tests proved of clinical value.

The patient, aged 51 years, had had seven children. Her menstrual periods were quite regular and normal including the last ten weeks before admission. Her symptoms on admission were: Four weeks' nausea, no vomiting; ten days' slight vaginal bleeding; three days' bleeding more severe; part of hydatidiform mole spontaneously aborted during the few hours preceding her admission.

Pregnancy tests on day after admission. Quantitative Zondek-Aschheim: Urine undiluted, positive in three out of four ovaries: diluted 1/25, 1/100 and 1/200 negative.

Two days after the urine was taken for the above tests Mr. Eardley Holland explored the uterus. The uterine sound passed four inches, a blunt curette removing no tissue resembling the hydatidiform mole.

Four weeks after evacuation of the mole the patient remained well. Flooding—much more than a normal period one week before—now ceased.

Pregnancy tests: Quantitative Zondek-Aschheim: Undiluted, negative; diluted, 1/25, 1/100 and 1/200, negative.

Patient readmitted. Uterus explored; strips of rather thick endometrium removed by sharp curette. No evidence of chorion-epithelioma.

In view of these findings, and of her age (51 years), a menopausal dose of radium (80 mgm. for twenty-two hours) was inserted in the uterus. Histological report on this curettage: Hæmorrhage into fragments of hyperplastic endometrium.

Thirty-nine weeks after the evacuation of the mole: Patient very well; good colour; gaining weight; complete amenorrhœa since curettage and radium treatment.

Pregnancy test: Friedman, negative.

Table II summarizes the pregnancy tests findings in this case.

TABLE II.—PREGNANCY TESTS FINDINGS IN CASE 72

Time when pregnancy tests were made	Results: Friedman	Results: Zondek-Aschheim		
	1/1	1/25	1/100	1/200
Day after spontaneous evacuation of mole	+	−	−	−
Blunt curettage				
4 weeks after the evacuation of the mole	−	−	−	−
Sharp curettage and menopause dose of radium				
39 weeks after the evacuation of the mole	−			

Additional case of hydatidiform mole. (Case 73.)

I. A., aged 26. Two children, the second over four years ago. Both labours normal. No miscarriages. Last menstrual period, August 16, 1934. First attended antenatal out-patients February 19, 1935 (that is after six months' amenorrhœa). Small show when periods expected during first three months of this time; then amenorrhœa until one week before admission. Severe bleeding at night and slight bleeding each day since then. No fœtal movements felt by patient. Urine clear. Fundus uteri twenty weeks. No fœtus felt. Cervix closed. Nothing abnormal felt in pelvis. X-ray examination: No evidence of fœtus. Friedman test positive. Quantitative Zondek-Aschheim: Positive, undiluted 1/25, 1/100, 1/200. February 26, admitted to London Hospital. Fundus uteri 2 inches above umbilicus. No clinical signs of fœtus. Quantitative Zondek-Aschheim: Positive, 1/200, 1/400, 1/800. February 28, two laminaria tents in cervix; vagina packed. March 1, small glycerine pig's bladder in uterus. March 2, bladder and mass of mole spontaneously expelled. Catheter specimen of urine, cloud of albumin, acid. Culture: *Staphylococcus albus*; many red cells and excess of leucocytes; epithelial cells. March 3, more mole expelled. March 4, Friedman test positive.

CHORION-EPITHELIOMA

Since 1912, 16 cases of chorion-epithelioma have been admitted to the London Hospital, and they have been classified into the following groups.

Cases of Chorion-epithelioma admitted to the London Hospital since 1912.

Following a hydatidiform mole pregnancy	6 cases.
Following an abortion	3 ,,
Following full-time normal pregnancy and labour ..	3 ,,
Occurring in males	2 ,,
No primary in genital tract	1 case.
Notes missing	1 ,,
	16 cases.

The 6 cases of chorion-epithelioma following hydatidiform mole pregnancies have already been considered.

In 3 cases (7, 8, 9) the chorion-epithelioma developed after a recent abortion, the exact nature of which was unknown. The abortion in each case may have been a hydatidiform mole, but there is no macroscopic or microscopic evidence or definite clinical history to establish the facts.

Case 7.—Patient, aged 19 years. Four months' miscarriage eleven months before admission. Baby present and two weeks later (during which time there was continuous bleeding) patient passed a large lump from the vagina like a "bunch of grapes." One month later curetted because of bleeding and floodings. Nine months after the miscarriage again curetted at a different hospital. Chorion-epithelioma was diagnosed and a subtotal hysterectomy, with removal of all appendages, was performed. Eleven months after the miscarriage and fourteen days before her death she was admitted to the London Hospital very ill; bleeding from the vagina. Normal cervix felt; bimanual examination impossible; very anæmic; progressive deterioration in vision; unconscious twenty-four hours before death.

Post-mortem examination revealed: Chorion-epithelioma of cervix; cerebral softening from obstruction of left middle cerebral artery by a malignant growth embolus; multiple secondary deposits in lungs, spleen, jejunum, &c.

Case 8.—Patient, aged 26 years; one child. Three months before admission, miscarriage at three months. Last menstrual period one month later—that is, two months before admission. No vaginal bleediug or discharge since then. For several weeks, repeated attacks of slight hæmoptysis, coughing up small clots of blood. Four hours before admission, awakened by severe lower abdominal pain. Vomited once; no vaginal bleeding. After admission: evidence of progressive intraperitoneal hæmorrhage. Cystic swelling in pelvis not altered by catheterization. Laparotomy revealed a large quantity of free blood in peritoneal cavity. Ragged hole in anterior wall of pouch of Douglas, through which grape-like structures were protruding. Cavity packed with flavine gauze; abdomen closed. Patient died before a blood transfusion could be given.

Post-mortem report: Hæmoperitoneum. Chorion-epithelioma in floor of pouch of Douglas. No growth in uterus, Fallopian tubes, or ovaries. Small secondary nodule in anterior wall of vagina close to outlet. Small secondary nodules in lungs, with attempt at villus formation.

Case 9.—This is the only case of chorion-epithelioma not definitely preceded by hydatidiform mole, in which the pregnancy test was employed as an aid to diagnosis.

Patient, aged 26 years. Two children, the second three and a half years ago. Twelve months before admission two months' miscarriage, followed by irregular bleeding for one month. Then, after two months' amenorrhœa, irregular uterine bleeding began, necessitating curettage on two occasions. Six weeks before admission, sudden onset of severe convulsions when out walking; chloroform used to control them. Jacksonian epilepsy, worse on right side; diplopia followed for several hours. Since then almost incessant headaches, and for three days, nausea and vomiting.

On examination.—Thin, healthy-looking. Wassermann reaction negative. Slight nystagmus, right greater than left; no papillœdema; intention tremor—right hand. Cerebrospinal fluid normal. Signs of increasing intracranial pressure developed.

Seen by Mr. Eardley Holland at the request of Mr. Hugh Cairns. Mr. Holland made the following note: "Uterus enlarged to size of eight weeks' pregnancy and soft swelling in region of right ovary, probably ovarian, size of a golf ball. It is possible that the patient has a chorion-epithelioma of the uterus with a secondary intracranial deposit. In this case swelling of the right ovary would be a compound lutein cystoma. A Zondek-Aschheim test should be done to see if an excess of the anterior pituitary-like hormone is present. A positive result would confirm the diagnosis of chorion-epithelioma."

Urine was sent the next day to the Pregnancy Diagnosis Station, Edinburgh, and the following report on it was received: "We have examined the specimen of urine and have found that the concentration of gonadotrophic hormone is very high, dilutions of 1 in 200, giving positive reactions when the normal doses are employed. This result supports your diagnosis of chorion-epithelioma."

Fourteen days later a pan-hysterectomy was performed by Mr. Holland because of the records published from time to time of the spontaneous disappearance of secondary chorion-epithelioma deposits on the removal or destruction of the primary growth. No such good fortune attended this patient, and in spite of post-operative treatment with lead selenate she died in coma about three weeks later. A post-mortem confirmed the diagnosis. Multiple deposits of chorion-epithelioma in the lungs, a small secondary deposit of chorion-epithelioma in the myocardium of the left ventricle, and a large secondary deposit of chorion-epithelioma in the brain were found.

Chorion-epithelioma following full-time normal pregnancy and labour. The three cases in this series all ended fatally.

Case 10.—Patient, aged 32; second child born seven and a half months before admission. No miscarriages. Continuous blood-stained vaginal discharge since the labour. Fourteen days' pain in the back on walking. Stony hard, fixed mass, about the size of a cricket ball, fixed low down on the right side of the pelvis. Laparotomy (H.R.A.) under the diagnosis of pyosalpinx. Chorion-epithelioma found, perforating the uterus and adherent to the right pelvic wall. Profuse hæmorrhage when fundus was lifted up. Subtotal hysterectomy. Patient died half an hour after operation, apparently from internal hæmorrhage. No post-mortem examination. Uterus not available.

Histological report.—Chorion-epithelioma involving endometrium and serosa of body and external os of cervix uteri.

Case 11.—Single woman; five months before admission had had a stillborn child. No miscarriages. Blood-stained vaginal discharge since birth of child. Necrotic mass, size of a large mushroom, attached by a fleshy pedicle to the back of a moderate cystocele. Cervix normal. (? Sloughing vaginal fibroid dissected away as in anterior colporrhaphy).

Histological report.—Chorion-epithelioma malignum in vagina.

Readmitted three and a half months later with vesico-vaginal fistula. Growth palpable in posterior wall of uterus. Vaginal hysterectomy. Subsequently mass developed in right iliac fossa. Histological report on uterus: Chorion-epithelioma of body of uterus. Patient developed progressive cachexia and died eleven months after labour, and six months after first operation. At post-mortem examination secondary deposits of growth were found in both lungs, in addition to growth in pelvis adjacent to hysterectomy scar.

Case 12.—Patient, aged 29. No miscarriages. Third labour six weeks before admission. Since then recurrent attacks of uterine hæmorrhage. Uterus explored twice, the second time four days before admission. Very anæmic. Third curettage was one month after admission: much débris removed—? placenta.

Histological report.—Fragments of chorion-epithelioma from body of uterus.

One week later pan-hysterectomy with removal of all appendages (H.R.A.). After removal of uterus nodule of growth seen on anterior wall of rectum. After operation patient had intermittent pyrexia and two rigors. She died five weeks later—that is, nearly four months after her last labour.

Post-mortem examination revealed acute fibrino-purulent endocarditis, pyæmia, purulent pelvic cellulitis, chorion-carcinoma of upper edges of vaginal stump, secondary deposits of growth in lungs and one femur.

Chorion-epithelioma in males.

Case 13.—Patient, aged 24. Swelling of right testis since an injury three months before admission. Two weeks—nausea, vomiting, loss of appetite, headaches, vertigo and diplopia.

On examination.—Pale, ill man, with a solid tumour of right testis, size of a fist; no thickening of cord; upper motor neurone paresis of left side of face. Death.

X-ray examination.—Shadows of secondary deposits in left lung.

A post-mortem examination revealed a teratoma, 9 × 7 × 9·5 cm., replacing the right testis. Microscopically, areas in this tumour showed the typical appearance of chorion-epithelioma. There were multiple secondary deposits of chorion-epithelioma in the lungs and a single large similar deposit in the cerebellum.

Case 14.—Patient, a man, aged 23, had complained for six months of increasing pain in the back, recently spreading into the legs. Marked cachexia and loss of weight. Intermittent pyrexia up to 102° F. Many lumps palpable in the abdomen. Clinical diagnosis—retro-peritoneal sarcoma. Death from cachexia.

Post-mortem report.—Very small teratoma in the centre of the right testis and multiple secondary deposits of chorion-epithelioma in the liver and in the lungs.

In the two remaining cases the case-records make no mention of previous pregnancies or of menstruation.

Case 15.—Patient, aged 49, admitted into a surgical ward with the following history:—

One month ago, severe attack of pain in right hypochondrium radiating into right shoulder and arm, lasting a week. Progressive loss of weight. Recurrence of pain with vomiting four days ago. Rigidity and tenderness in right hypochondrium led to an exploratory laparotomy. Large cystic swelling found in liver. Aspiration yielded pure blood; much blood-stained fluid in peritoneal cavity. Growth palpable in other viscera and in pouch of Douglas. Abdomen closed. Four days later, normal period occurred, and seven weeks later patient died.

Post-mortem examination revealed multiple secondary deposits of chorion-epithelioma in the liver and other organs. No definite primary focus could be identified in the genital tract or elsewhere.

Case 16.—Patient, aged 30. No notes available. Diagnosis—pneumonia. Died day of admission after laparotomy.

Post-mortem findings.—Anæmia from hæmorrhagie; hæmoperitoneum (1½ pints).

Perforation by chorion-epithelioma of a uterus greatly enlarged by masses of growth in its right wall (14·5 × 10 × 6·5 cm.).

Three perforations of growth into the peritoneal cavity and one into right vaginal fornix. Secondary deposits of growth in both lungs. Direct invasion by growth of right ovary and trigone of bladder.

SUMMARY

One case of combined normal gestation and a molar gestation suggests that the ætiological factor is probably an inherent abnormality of the ovum and not of the mother.

Molar gestations occur at all child-bearing ages, but in this series 37·5% occurred in women 40 years of age or more.

The average previous fertility is 4·3 children and 0·7 miscarriages, but 23·6% were primigravida.

In about 20% of cases the uterus is smaller than the calculated duration of pregnancy would lead one to expect.

In 35% of 34 cases where the examination was recorded in catheter specimens there was albuminuria.

The commonest error in diagnosis was pelvic tumour (uterine or ovarian) in 12·5% of the cases. The majority were over 40 years of age.

Conservative treatment was adopted in the majority of cases (primary hysterectomy in 6 cases only) and resulted in a very low mortality (1 case), i.e. 1·4%.

Puerperal septicæmia or pyæmia developed in 6 cases. 9% of these subsequently developed chorion-epithelioma.

Secondary hæmorrhage during the puerperium occurred in 15% of the cases. Out of a total of 10 cases that developed this complication 4 were due to the development of chorion-epithelioma in the uterus.

Two other cases of chorion-epithelioma are known to have developed, neither of which developed secondary hæmorrhage.

Thus the incidence of chorion-epithelioma known to have occurred in this series was 6, i.e. 8·3%. One of these 6 cases was a malignant perforating hydatidiform mole.

Eight other cases of chorion-epithelioma occurred during the same period of years, 2 of them being in males.

The value of the pregnancy tests of Zondek-Aschheim and Friedman is illustrated and the importance of assessing them in relation to the other clinical and laboratory findings is stressed.

The ultimate prognosis of cases with proved chorion-epithelioma is unexpectedly good in this series.

Fertility after a hydatidiform mole pregnancy is frequently perfectly normal.

My sincere thanks are due to Mr. Eardley Holland, Mr. Victor Lack, and other members of the London Hospital Honorary Consulting Staff, for the use of their case-records.

[*A pathological demonstration of macroscopic and microscopic specimens was arranged to illustrate such cases as had particular interest.*]

Discussion.—Mr. J. B. BLAIKLEY said that he had recently seen eight cases of hydatidiform mole and had noticed how varied the symptomatology had been. Three patients had shown gross albuminuria and a high blood-pressure, one of the three was œdematous from the waist down and had a great deal of ascites; another had been operated upon for torsion of an ovarian cyst and forty-eight hours later she aborted a vesicular mole. Obviously the cyst was a lutein cyst. In two of the eight cases severe sepsis had followed in one, an acute infection of the uterus with *Bacillus welchii* was treated with serum, the patient had almost recovered.

The following case would probably be of interest. A 2-para complained of four weeks' continuous loss following seven weeks' amenorrhœa, diagnostic curettage was carried out and a hæmorrhagic piece of tissue removed, while bimanual examination showed a soft swelling attached to the left side of the uterus. Microscopic examination showed a rare variety of hydatidiform mole in which the vesicles were surrounded by fibrous tissue six or seven cells deep. In view of the swelling felt, a Friedman test was made and on more than one occasion during the following month gave a negative reaction. However, as the swelling had increased in size it was decided to readmit the patient to Guy's Hospital for laparotomy, Operation showed the isthmus of the Fallopian tube and the cornu of the uterus to be distended by what appeared to be a hæmorrhagic tumour, total hysterectomy was performed and the left appendage removed. Microscopic examination showed the mass to consist of a few villi and much blood-clot. This case was of particular interest, if for no other reason than the fact that the pregnancy test was negative. The converse of this case was that of a primigravida, who gave a history of six weeks' amenorrhœa followed by ten weeks' slight

bleeding, and was found to have an asymmetrical uterus enlarged up to the umbilicus. The Friedman test produced a positive reaction in dilutions of 1 : 2000, which was thought to be conclusive evidence of hydatidiform mole and abdominal hysterotomy was performed ; an angular pregnancy was found, but apart from blood between the membranes and some hydramnios, it was normal ; the uterus was curetted through the incision. The Friedman reaction remained positive in dilutions of 1 : 200 for fourteen days but was negative after a month. These two cases bore out what Mr. Brews has said about caution in assessing the results of a pregnancy test in the diagnosis of this condition. Dr. P. M. F. Bishop who performed the Friedman tests at Guy's Hospital had reported 300 consecutive tests with only two erroneous results.

He differed from Mr. Brews in accepting a case of perforating mole as one of chorion-epithelioma, as he did not consider perforation of the uterus to be evidence of malignancy. It had been shown that the mole eroded the wall of a vein and ramified along the lumen until it came to lie under the peritoneum, when it might again erode the thin wall of the vein, and also the peritoneum, quite easily. There was no true perforation of the muscular wall of the uterus.

Professor JAMES YOUNG said that Mr. Brews had raised the question as to whether a true malignant condition was possible in hydatid mole. Professor James Miller, some years ago, had reported a case in which after death masses of tissue were found in the lungs which consisted of chorionic villi exhibiting marked invasive properties. This case was reported in the *Transactions of the Edinburgh Obstetrical Society.*

With regard to the occurrence of hydatid mole in one placenta of binovular twins, he (Professor Young) had had a case of this nature some years ago. Both fœtuses were present and, whilst one placenta was apparently normal, there was an area of hydatid change affecting the other.